AD_____

Award Number: DAMD17-96-1-6319

TITLE: Risk Factors for Osteoporosis and Oral Bone Loss in Postmenopausal Women

PRINCIPAL INVESTIGATOR: **Jean Wactawski-Wende, Ph.D.**

CONTRACTING ORGANIZATION: State University of New York at Buffalo
Amherst, New York 14228-2567

REPORT DATE: October 2000

TYPE OF REPORT: **Annual**

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2000	Annual (16 Sep 99 - 15 Sep 00)

4. TITLE AND SUBTITLE
Risk Factors for Osteoporosis and Oral Bone Loss in Postmenopausal Women

5. FUNDING NUMBERS
DAMD17-96-1-6319

6. AUTHOR(S)
Jean Wactawski-Wende, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
State University of New York at Buffalo
Amherst, New York 14228-2567

E-MAIL:
jww@acsu.buffalo.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

The overall purpose of this study is to determine the relationship between skeletal and oral bone density, identify factors influencing bone loss, and determine the relationship between osteoporosis and oral bone loss, periodontal disease and tooth loss. We hypothesize that reduction in bone density leading to osteoporosis, plays a significant role in increasing susceptibility to destructive periodontitis and tooth loss. Sensitive and accurate measures of skeletal and oral bone mineral density, periodontal disease and tooth loss will be used. A wide variety of other risk factors for both osteopenia and periodontal disease will be assessed. Over 1300 subjects are being recruited from an ongoing NIH funded study cohort, the Women's Health Initiative (WHI). This year preliminary findings were presented at the World Congress of Osteoporosis (June, 2000; Chicago). Data were presented for the first 608 study participants enrolled from the larger study of over 1400 women. These analyses found that lower skeletal bone mineral density (BMD) is related to poorer alveolar crest height. In addition, in a second analysis we found moderate alcohol intake to be associated with higher BMD.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Osteoporosis	15
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

TABLE OF CONTENTS

INTRODUCTION

The overall purpose of this study is to determine the relationship between skeletal and oral bone density, identify factors influencing bone loss, and determine the relationship between osteoporosis and oral bone loss, periodontal disease and tooth loss. We hypothesize that reduction in bone density leading to osteoporosis, plays a significant role in increasing susceptibility to destructive periodontal disease and tooth loss. Sensitive and accurate measures of skeletal and oral bone mineral density, periodontal disease and tooth loss are used in this study. A wide variety of other risk factors for both osteopenia and periodontal disease will be assessed as part of this study. Over 1300 subjects are being recruited from an ongoing NIH funded study cohort, the Women's Health Initiative (WHI), making this an efficient and cost effective study. A limited number of studies have assessed bone loss in the oral cavity and have suggested that low bone density is associated with severe periodontal disease. However, these studies have been plagued with small sample sizes and poor assessments of confounding factors such as smoking, alcohol intake, and age, among others. Our study will assess these factors in detail. This year preliminary findings were presented at the World Congress of Osteoporosis (June, 2000; Chicago - See Appendix for copies of the abstracts). Data were presented for the first 608 study participants enrolled from the larger study of over 1400 women. These analyses found that lower skeletal bone mineral density (BMD) is related to poorer alveolar crest height. In addition, in a second analysis we found moderate alcohol intake to be associated with higher BMD.

The U.S. population is projected to include an increasing proportion of older men and women in the next few decades, including retired and active military personnel. Hence, management of two of the most common chronic diseases in older persons, osteoporosis and periodontal disease, will demand increasing health service resources. New approaches to prevention, early diagnosis and intervention of these diseases are critical. The proposed study has great practical significance. If oral bone loss is a predictor of low skeletal bone, those people detected on a dental exam to have oral bone loss could be targeted for further evaluation for osteoporosis. Interventions could be started to prevent further bone loss or fracture. Conversely, those with weak skeletal bones may need evaluation for oral bone loss, preventing further loss of bone and

subsequent tooth loss. This study potentially provides a new approach to screening for osteoporosis. Last, treatments affective for osteoporosis may prove useful in the prevention and treatment of oral bone and tooth loss.

BODY

This is an ongoing epidemiologic study entitled "Risk Factors for Osteoporosis and Oral Bone Loss in Postmenopausal Women". Data collection is ongoing and will continue through the Fall of 2000. Data clean-up has been ongoing and is continuing. The final analytic dataset will be ready in the next 2 months. Data analysis and preparation of publications will be the focus of the remainder of this coming year. The body of this report will highlight the methods, assumptions and procedures used for data collection, provide detail on data collection through 09/15/00 and provide specific information regarding tasks proposed in the outline of work.

Experimental Methods, Assumptions and Procedures:

Population to be studied. Subjects for the dental examination and dual-energy x-ray absorptiometry (DXA) are being recruited from the participants in the Women's Health Initiative. The Women's Health Initiative (WHI) is a major research effort to study methods of disease prevention and health promotion among postmenopausal women. It includes a Clinical Trial and Observational Study (OS). Only women enrolled in the OS will be recruited to join this study. The WHI Observational Study (OS) includes postmenopausal women aged 50-79 years at baseline who were unwilling to participate or ineligible for the CT. As part of WHI the women have many baseline measurements, with clinical outcomes determined at annual intervals. The objectives of the OS are to obtain better estimates of the predictive ability of known risk factors for disease, to unearth new risk factors and biomarkers for disease, and to examine the relationship of change in characteristics to prevalent and future disease. In Buffalo, a total of 2248 women have enrolled into the OS. Women agreeing to participate in the Observational Study will be followed for an average of 9 years by the WHI staff. Baseline data collected as part of the OS will be related to putative risk factors and protective factors.

The current study, "Risk Factors for Osteoporosis and Oral Bone Loss", will add a bone density scan and an oral examination to the Buffalo WHI OS protocol, assess the prevalence and severity of osteopenia in this cohort of women, and evaluate osteopenia's role in development of periodontal disease/oral bone loss, and assess risk variables common or unique to each disease.

Subject recruitment. Subjects are being recruited from the WHI Observational Study participants. Women who are enrolled in the WHI Observational Study are contacted by mail and given information about the Osteoporosis/Oral Bone Loss study and asked to participate. A recruitment tool is the offer of a free bone density assessment and dental/oral health examination. Each woman who expresses interest in the study is initially given a brief telephone eligibility screen. Those determined eligible are appointed for a clinical examination.

Of th2 2,248 women enrolled in the WHI OS, 1400 or more are expected to participate in this study. To date, recruitment into this study has been extremely successful. Details of subject recruitment as of 09/15/00 are presented in "Results and Discussion" section of this report.

Mailing. Women who have already entered the WHI OS study are contacted by mail and asked to call our center if they are interested in learning more about participating. When they call, these women are told about the osteo/dental study, given an opportunity to ask questions, and those who are interested are given a brief eligibility screen.

Eligibility Screen. Information collected on the eligibility screen concern criteria for both DXA and dental assessments. DXA scan exclusion criteria include recent use of contrast agents and known aortic calcification, steroid dependency (use of systemic steroids for the past 6 months), and active cancer or cancer chemotherapy. Criteria for the Periodontal exam are that subjects have at least 6 teeth and have had no periodontal surgery in the last 3 months. Age (50 to 79) and postmenopausal status have already been met as part of WHI. All eligible women are informed that they will be required to sign an informed consent prior to DXA and dental examinations. If women are determined to be both eligible and interested, they are scheduled for an appointment and sent a study packet by mail. The study packet includes information on temporary exclusion criteria to be aware of (i.e. contrast agents), study questionnaires to be

completed at home and brought to the study visit, the consent form to read and review, instructions on what to wear and bring with them, information on premedication (if necessary), and a parking pass for the visit.

Examinations and Testing. At the time of the appointment, a DXA scan is performed by a trained and certified x-ray technician. All subjects accepted into the study receive a measurement of bone mineral density by DXA. The DXA sites will include the lumbar spine, femur and forearm, as well as a determination of whole body composition (fat, lean, mineral content). As part of the oral examination, all subjects receive a complete head and neck and intraoral examination with assessment of periodontal disease by both probing depth and assessment of alveolar crestal height. In addition, mandibular bone density is assessed using a stepwedge radiographic technique.

Before examination begins, participants are required to sign an informed consent form which is reviewed with the participant by a member of the staff. Questions are answered on risks, benefits, voluntary participation and confidentiality.

Questionnaires are self-administered and brought to the visit. At the time of the visit the questionnaires are reviewed by study personnel for completeness and accuracy. Participants can request assistance in completing the questionnaires if needed. Additional information (not collected as part of WHI) on osteoporosis risk factors, oral health history, current medication intake and personal habit history are included in the questionnaires.

The **DXA exam** includes: AP/Lateral Assessment of the Lumbar Spine Density (L1, L2, L3 and L4); Femur Density Assessment (femoral neck, Ward's Triangle, trochanteric region, inter-trochanteric region, and total region); Forearm; and Body Composition Assessment (total body skeletal density, fat and lean).

The **Oral Health Examination** includes examination of the head and neck, and oral mucous membranes. Record of restorative appliances, as well as coronal and root caries, and missing teeth are done. Measurements include: plaque assessment, gingival assessment, calculus

index, pocket depth measurement, and clinical attachment level (Florida probe). Oral radiographs include periapical x-rays for alveolar crestal height (ACH), and mandibular basal bone mineral density (MBMD). Radiographs are taken using a standardized techniques and measured using a computer-assisted technique using a method, training and calibration procedure developed by Dr. Hausmann and successfully applied locally. Samples of saliva, plaque and blood are collected and frozen.

Results and Discussion:

Analysis of study data and report of final results will not be available until the end of the coming year. However, two interim analyses were conducted on 608 subjects. Results of these analyses were presented at the World Congress of Osteoporosis (June, 2000) and are included in the Appendix of this report. Outlined below is a detailed report of our recruitment experience as of the end of year-4. As of 09/15/00 a total 2249 letters have been sent to WHI OS participants. Of these, 1399 women have completed participation in this study. In addition, 35 women are scheduled to participate. We have exceeded our recruitment goal of 1300 enrollees and plan to allow all those scheduled with an appointment to enroll. It is expected that approximately 1430 will be enrolled by November, 2000. Further detail on recruitment is presented below.

Recruitment Summary as of 09/15/00

WHI OS Participants Contacted:

2249 Total letters sent to date (All WHI OS participants have been contacted)

Visits Completed, Willing and Eligible:

1399 Visits completed/enrolled
35 Appointments scheduled

No Contact, Ineligible, Not Interested:

35 No contact/no response
4 Undecided
34 Temporarily ineligible but interested (i.e. recent contrast agent, out of town)
32 Need to reschedule due to cancellation
275 Not interested
50 Deceased
260 Ineligible

Recent Letters, no contact to date:

92 Recent letters, unable to contact to date

Recommendations In Relation To The Outline Of Work:

The Timeline/Statement of Work from our proposal/funding application is presented below. For each of the tasks, a description of what has been completed and the relation to the timeline are described. In general, tasks have initiated and/or completed within the proposed time frame. When the time frame differs, an explanation is provided.

Proposed Timeline From Application:

Task 1: **Months 1-3^{+}:** Hire personnel, complete training and certification (Nurse mgr, DXA tech, Dental Fellow, clerk, data mgr.)

We have hired, trained and certified a number of staff and key personnel. The personnel who have been employed either on the grant or as *in kind* contributions to the grant during the past 12 months are:

Staff Name	Position
Jean Wactawski-Wende, PhD	Principal Investigator
Robert Genco, DDS PhD	Co-Investigator
Sara Grossi, DDS MS	Co-Investigator
Ernest Hausmann, DMD PhD	Co-Investigator
Maurizio Trevisan, MD MS	Co-Investigator
Cheryl Klemenz	Project Manager/Data Manager
Laurie Barrick	DXA Technician
Dorothy Wright	Secretary/Data Clerk
Sharon Chory	Data Entry
June Markello	Dental Hygienist/Assistant
Mine Tezal, DDS MS	Dentist/Examiner
Marcelo Araujo, DDS	Dentist/Examiner
Linda Roth	Dental Hygienist/Assistant
Patricia Gill	Dental Hygienist/Assistant
Jan Benedek	Dental Hygienist/Assistant
Steve Lancaster	Dental Hygienist/Assistant
Robert Dunford, MS	Dental Data Manager
Kathleen Hovey, MS	Data Analyst
Jolie Weiss, MS	Doctoral Student
Renee Brennan, BA	Master Student
Jennifer Rescke, BA	Master Student
Walter Iwanenko, MS	Doctoral Student

All staff have been trained to conduct their respective duties and certified All investigators are actively involved in the project activities and meet regularly to discuss all aspects of the study. Investigators include Drs. Wactawski-Wende, Genco, Grossi, Hausmann, and Trevisan.

Task 2: **Months 1-3:** Identify OS participants from WHI database
Link study files to WHI OS participant files

The roster of all Observational Study participants from the WHI was extracted and a participant database was created for this study. This database has been used for all study mailings and contacts. It is updated periodically from the WHI roster to insure accuracy of address and other contact information. A separate data file has been completed to enter all clinical and questionnaire information we collect during the study. The data files are separate from the files which include patient identifiers for confidentiality reasons, linked by an study identification number.

Task 3: **Months 2-4:** Finalize study questionnaire; pilot test questionnaire

The questionnaires have been completed and approved for use by both our local IRB and the Army IRB. The questionnaires are completed by all participants. The information included on these questionnaires are supplemental to that already collected as part of WHI.

Task 4: **Months 4-6:** Preparation of initial sample mailing and contact to test contact procedures

Conduct pilot testing of examination procedures on sample of OS participants

Create computerized data files for entry of questionnaires and non-computerized clinical data

As reported in the first annual report, sample mailings were conducted in 80 subjects. This process was very useful in determining timing of appointments and logistics for conducting the study. It was also useful for training and certification of staff. The data entry files have been created and data entry is ongoing. The contact letter, screening questionnaires and consent were approved by the Army Human Use and University at Buffalo IRB.

Task 5: **Months 6-7**: Evaluate and revise procedures based on pilot sample

Procedures were evaluated and some revisions of the original grant were requested and received which have been implemented (i.e. blood, saliva and plaque collection; forearm scan). Procedures were set in year 2 and continue to be implemented.

Task 6: **Months 7-40:** Begin weekly mailings to approximately 70 women

Weekly have begun sent and all 2249 WHI OS participants have been contacted by mail. Details of the results of mailings are presented in "Results and Discussion".

Task 7: **Months 8-40:** Conduct eligibility screens on interested participants

Obtain informed consent

Conduct DXA/Dental evaluations and have participants complete study questionnaires

Continue quality control procedures throughout study to ensure quality of examiners

In an ongoing fashion we have been completing eligibility screen, scheduling appointments for those interested and eligible, obtaining informed consent, conducting both the DXA and dental examinations, collecting questionnaire information, and continuing quality control of all examining staff. As of 09/15/00 a total of 1399 women have completed participation in the study. Task 7 activities will continue into the Fall of 2000 to allow remaining interested women to participate.

Task 8: **Months 9-42:** Entry of questionnaire data and verification

Data management of computerized files

Entry and verification of the study data has been ongoing. The computerized files for data entry have been created and are in use. The data from both the DXA scan and Dental exam are directly entered at time of visit and will be merged with questionnaire and WHI data when analysis is started. Back up copies of all data files are kept daily. Over the next year, the final data files will be merged. Intensive data checking and verification is currently being conducted. A final cleaned data set with all enrollees information will be available in the next two months.

Task 9: **Months 40-48:** Begin preliminary data analysis; conduct multivariate analysis

Begin manuscript preparation

Inform participants of initial findings of the study

Preliminary analyses have been conducted on a subset of the cohort (see Appendix). Once data collection, data entry and data verification is complete, analysis of the final data set will be conducted. Analysis of the data, preparation of manuscripts and presentation of the results will be the focus of the coming year of this study.

Research Accomplishments:

- Successful enrollment of 1399 study subjects to date (exceeded recruitment goal of 1300)
- Presentation of preliminary results (2 poster presentations) at a national meeting

Reportable Outcomes:

- Training and participation of dentist-scientists in research design, methods and implementation. The following have participated:

Mine Tezal, DDS MS
Marcelo Araujo, DDS
Michael Lynch, DMD
Jeffrey Rogers, DDS
Jim Katancik, DDS, PhD

Drs. Tezal and Araujo will continue training in the coming year.

- Drs. Tezal and Araujo enrolled in the PhD program in Epidemiology and Community Health.
- A PhD project ongoing for Walter Iwanenco, Doctoral student in Epidemiology and Community Health using a portion of this data.
- Hands-on training for graduate students in study implementation including:
    - Renee Brennan
    - Jolie Weiss
    - Jennifer Rescke
    - Cheryl Klemenz

- Funding has been applied for to the NIH for the study entitled "Bone Mineral Density as a Predictor of Periodontitis". This longitudinal study is planned to follow women enrolled in this study.
- A repository of blood, saliva and plaque has been established. The samples were collected as part of this study. Samples are stored in liquid nitrogen awaiting analysis.
- To date, 2 abstracts have resulted from this grant.

CONCLUSIONS

Fianl results of this research will not be available until the coming year, however the importance and implications of this study are many. The proposed study has great practical significance since if oral bone loss is a predictor of skeletal bone loss, those women who are detected on dental exam to have oral bone loss could be targeted to have further evaluation of skeletal bone density to determine their risk of osteoporosis. These women could then be targeted for interventions which could prevent progression and/or future fracture. Conversely, women with severe skeletal osteopenia may need to be evaluated for risk of oral bone loss, in order to target interventions to prevent progression and subsequent tooth loss. This study potentially provides a new approach for screening for women at risk for osteoporosis.

APPENDIX

Published Abstracts/Poster Presentations:

AVERAGE TOTAL ALCOHOL INTAKE AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN

J. Wactawski-Wende, M. Trevisan, R. Brennan, S.G. Grossi, R.J. Genco, C. Klemenz
University at Buffalo, Buffalo, NY, USA
World Congress of Osteoporosis, Chicago, IL. June 15, 2000.

THE RELATIOSHIP OF BONE MINERAL DENSITY TO ORAL BONE LOSS IN POSTMENOPAUSAL WOMEN

J. Wactawski-Wende, S.G. Grossi, E. Hausmann, R. Dunford, R.J. Genco, C. Klemenz, M. Trevisan, University at Buffalo, Buffalo, NY, USA
World Congress of Osteoporosis, Chicago, IL. June 15, 2000.

AVERAGE TOTAL ALCOHOL INTAKE AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN

J. Wactawski-Wende, M. Trevisan, R. Brennan,
S.G. Grossi, R.J. Genco, C. Klemenz
University at Buffalo, Buffalo, NY, USA

This study assesses the relationship between average total alcohol intake and bone mineral density (BMD) in 608 Caucasian post-menopausal women from Buffalo, NY participating in a larger study of the relationship between BMD and periodontal disease, an ancillary study of the NIH Women's Health Initiative. After consent, all women completed questionnaires on health history and risk exposure, and had a physical exam. BMD of the hip (total femur region) was assessed by dual energy X-ray absorptiometry (DXA; Hologic QDR-4500). BMD was dichotomized for logistic regression analyses (lowest tertile vs. highest 2 tertiles). Alcohol intake (mean daily ounces total alcohol) was the primary independent variable of interest. Other factors assessed in the analysis were: age at interview, cigarette smoking (ever), education ($\leq$high school, college, graduate school), body mass index (BMI), diabetes (ever), thyroid disease (ever), physical activity (daily hours standing), fracture $\geq$ age 40 (ever), and years of estrogen deficiency (years since menopause-years of estrogen replacement therapy). Alcohol intake was found to be protective for lower BMD (OR=0.84, p=.1919). Other factors found to be associated with lower BMD included: history of adult fracture (OR=1.83, p=.0046), higher BMI (OR=0.86, p=.0001), older age (OR=1.06, p=.0026), and fewer years without estrogen (OR=1.04, p=.0011). This study supports the hypothesis that moderate lifetime alcohol intake is associated with higher BMD of the total femur, even after controlling for factors known or suspected to be associated with bone mineral density.

THE RELATIOSHIP OF BONE MINERAL DENSITY TO ORAL BONE LOSS IN POSTMENOPAUSAL WOMEN

J. Wactawski-Wende, S.G. Grossi, E. Hausmann,
R. Dunford, R.J. Genco, C. Klemenz, M. Trevisan, University at Buffalo, Buffalo, NY, USA

This study assesses the relationship between bone mineral density (BMD) and oral bone loss in 608 Caucasian postmenopausal women from Buffalo, NY participating in a study of BMD and periodontal disease, an ancillary study of the NIH Women's Health Initiative. After consent, women completed questionnaires on health history, risk exposures and had a physical exam. Oral bone loss was defined as mean loss of alveolar crestal height (ACH) dichotomized for logistic regression analyses (worst ACH tertile vs. best tertiles). BMD of the total femur (lowest vs. highest 2 tertiles) was the primary independent variable of interest and was assessed by dual energy X-ray absorptiometry (DXA; Hologic QDR-4500). Other factors assessed included: age at visit, cigarette smoking (ever), education ($\leq$ high school, college, graduate school), body mass index (BMI), diabetes (ever) and years estrogen deficiency (years since menopause - years on estrogen). BMD was found to be protective for loss of ACH (OR=0.64, p=.0630). Other factors independently associated with ACH loss included: older age (OR=1.07, p=.0005), ever smoking cigarettes (OR=1.69, p=.0069), fewer years without estrogen (OR=1.03, p=0.0245) and BMI (OR=0.96, p=0.0412). This study supports the hypothesis that lower BMD is associated with loss of oral bone even after controlling for factors known or suspected to be associated with either ACH or BMD. This study is one of the largest to date and supports previous findings by us and others that lower BMD is related to oral bone loss, that may lead to tooth loss. Additional research is needed to better understand this relationship.